However, reviews and studies[1,2] in patients with reflex sympathetic dystrophy failed to find any benefit from guanethidine.

1. Jadad AR, *et al.* Intravenous regional sympathetic blockade for pain relief in reflex sympathetic dystrophy: a systematic review and a randomized, double-blind crossover study. *J Pain Symptom Manage* 1995; **10:** 13–20.
2. Livingstone JA, Atkins RM. Intravenous regional guanethidine blockade in the treatment of post-traumatic complex regional pain syndrome type 1 (algodystrophy) of the hand. *J Bone Joint Surg Br* 2002; **84:** 380–6.

Preparations

BP 2008: Guanethidine Tablets;
USP 31: Guanethidine Monosulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Ismelin; ***Gr.:*** Ismelin; ***UK:*** Ismelin; ***USA:*** Ismelin†.

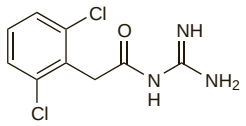
Multi-ingredient: ***Arg.:*** Normatensil†; ***Austria:*** Thilodigon†; ***Ger.:*** Esimil†; Thilodigon; ***Irl.:*** Ganda; ***USA:*** Esimil.

Guanfacine Hydrochloride *(BANM, USAN, rINNM)*

BS-100-141; Guanfacine, Chlorhydrate de; Guanfacini Hydrochloridum; Hidrocloruro de guanfacina; LON-798. *N*-Amidino-2-(2,6-dichlorophenyl)acetamide hydrochloride.

Гуанфацина Гидрохлорид

$C_9H_9Cl_2N_3O,HCl$ = 282.6.
CAS — 29110-47-2 (guanfacine); 29110-48-3 (guanfacine hydrochloride).
ATC — C02AC02.
ATC Vet — QC02AC02.



(guanfacine)

Pharmacopoeias. In *US.*
USP 31 (Guanfacine Hydrochloride). Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Clonidine Hydrochloride, p.1247. Rebound hypertension may occur but is delayed due to the longer half-life.

◊ Reviews.

1. Jerie P. Clinical experience with guanfacine in long-term treatment of hypertension, part II: adverse reactions to guanfacine. *Br J Clin Pharmacol* 1980; **10** (suppl 1): 157S–164S.
2. Board AW, *et al.* A postmarketing evaluation of guanfacine hydrochloride in mild to moderate hypertension. *Clin Ther* 1988; **10:** 761–75.

Withdrawal. Rapid reduction of the guanfacine dosage resulted in rebound hypertension leading to generalised seizures and coma in a 47-year-old patient with renal failure who was receiving haemodialysis.[1] Use with phenobarbital may have enhanced the metabolism of guanfacine and contributed to the development of the withdrawal effect.

1. Kiechel JR, *et al.* Pharmacokinetic aspects of guanfacine withdrawal syndrome in a hypertensive patient with chronic renal failure. *Eur J Clin Pharmacol* 1983; **25:** 463–6.

Interactions

As for Clonidine Hydrochloride, p.1248.

Pharmacokinetics

Guanfacine is rapidly absorbed after oral doses and peak plasma concentrations occur 1 to 4 hours after ingestion. The oral bioavailability is reported to be about 80%. It is about 70% bound to plasma proteins. It is excreted in urine as unchanged drug and metabolites; about 50% of a dose is reported to be eliminated unchanged. The normal elimination half-life ranges from 10 to 30 hours, tending towards the upper range in older patients.

Renal impairment. A study[1] in patients with normal or impaired renal function found that guanfacine clearance and serum concentrations were not significantly different in the 2 groups, suggesting that non-renal elimination plays an important role in patients with renal impairment.

1. Kirch W, *et al.* Elimination of guanfacine in patients with normal and impaired renal function. *Br J Clin Pharmacol* 1980; **10** (suppl 1): 33S–35S.

Uses and Administration

Guanfacine is a centrally acting alpha$_2$-adrenoceptor agonist with actions and uses similar to those of clonidine (p.1248). It is used in the management of hypertension (p.1171), although other drugs are usually preferred. It may be used alone or with other antihypertensives, particularly thiazide diuretics. It has also been tried in the management of opioid withdrawal and in hyperactivity disorders.

Guanfacine is given orally as the hydrochloride, but doses are usually expressed in terms of the base. Guanfacine hydrochloride 1.15 mg is equivalent to about 1 mg of guanfacine. In hypertension the usual initial dose is 1 mg daily increasing after 3 to 4 weeks to 2 mg daily if necessary.

◊ Reviews.

1. Cornish LA. Guanfacine hydrochloride: a centrally acting antihypertensive agent. *Clin Pharm* 1988; **7:** 187–97.

Tourette's syndrome. Guanfacine may be used as an alternative to clonidine in the management of patients with mild to moderate symptoms of Tourette's syndrome (see Tics, p.954). First-line use of these drugs is increasingly favoured in such patients because of a relative lack of serious adverse effects when compared with the commonly used antipsychotics.

Preparations

USP 31: Guanfacine Tablets.

Proprietary Preparations (details are given in Part 3)
Belg.: Estulic; ***Cz.:*** Estulic†; ***Fr.:*** Estulic; ***Hung.:*** Estulic; ***Jpn:*** Estulic†; ***Neth.:*** Estulic†; ***Rus.:*** Estulic (Эстулик); ***USA:*** Tenex.

Heparin *(BAN)*

Heparíini; Heparina; Heparinum; Heparyna.
CAS — 9005-49-6.
ATC — B01AB01; C05BA03; S01XA14.
ATC Vet — QB01AB01; QC05BA03; QS01XA14.

Description. Heparin is an anionic polysaccharide of mammalian origin with irregular sequence. It consists principally of alternating iduronate and glucosamine residues, most of which are sulfated. It may be described as a sulfated glucosaminoglycan. Heparin has the characteristic property of delaying the clotting of freshly shed blood. It may be prepared from the lungs of oxen or the intestinal mucosa of oxen, pigs, or sheep.
Heparin is often described in the literature as standard heparin or unfractionated heparin to distinguish it from low-molecular-weight heparins.

Heparin Calcium *(BANM)*

Calcium Heparin; Heparíinikalsium; Heparin Kalsiyum; Heparin Sodyum; Heparin vápenatá sůl; Heparina cálcica; Héparine calcique; Heparinkalcium; Heparino kalcio druska; Heparinum calcicum; Heparyna wapniowa.
CAS — 37270-89-6.
ATC — B01AB01; C05BA03; S01XA14.
ATC Vet — QB01AB01; QC05BA03; QS01XA14.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Heparin Calcium). The potency of heparin calcium intended for parenteral use is not less than 150 international units per mg and the potency of heparin calcium not intended for parenteral use is not less than 120 international units per mg, both calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers.
USP 31 (Heparin Calcium). The calcium salt of heparin with a potency, calculated on the dried basis, of not less than 140 USP units in each mg. USP heparin units are not equivalent to international units. The source of the material is usually the intestinal mucosa or other suitable tissues of domestic mammals used for food by man and should be stated on the label. A 1% solution in water has a pH of 5.0 to 7.5. Store in airtight containers at temperatures below 40°, preferably between 15 and 30°.

Incompatibility. See Heparin Sodium, below.

Heparin Sodium *(BANM, rINN)*

Hepariininatrium; Heparin sodná sůl; Heparina sódica; Héparine sodique; Heparinnatrium; Heparino natrio druska; Heparinum natricum; Heparyna sodowa; Sodium Heparin; Soluble Heparin.

Гепарин Натрий
CAS — 9041-08-1.
ATC — B01AB01; C05BA03; S01XA14.
ATC Vet — QB01AB01; QC05BA03; QS01XA14.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Heparin Sodium). The potency of heparin sodium intended for parenteral use is not less than 150 international units per mg and the potency of heparin sodium not intended for parenteral use is not less than 120 international units per mg, both calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers.
USP 31 (Heparin Sodium). The sodium salt of heparin with a potency, calculated on the dried basis, of not less than 140 USP units in each mg. USP heparin units are not equivalent to international units. The source of the material is usually the intestinal mucosa or other suitable tissues of domestic mammals used for food by man and should be stated on the label. A white or pale-coloured amorphous, odourless or almost odourless, hygroscopic powder. Soluble 1 in 20 of water. A 1% solution in water has a pH of 5.0 to 7.5. Store in airtight containers at temperatures below 40°, preferably between 15 and 30°.

Incompatibility. Incompatibility has been reported between heparin calcium or sodium and alteplase, amikacin sulfate, amiodarone hydrochloride, ampicillin sodium, aprotinin, benzylpenicillin potassium or sodium, cefalotin sodium, ciprofloxacin lactate, cytarabine, dacarbazine, daunorubicin hydrochloride, diazepam, dobutamine hydrochloride, doxorubicin hydrochloride, droperidol, erythromycin lactobionate, gentamicin sulfate, haloperidol lactate, hyaluronidase, hydrocortisone sodium succinate, kanamycin sulfate, meticillin sodium, netilmicin sulfate, some opioid analgesics, oxytetracycline hydrochloride, some phenothiazines, polymyxin B sulfate, streptomycin sulfate, tetracycline hydrochloride, tobramycin sulfate, vancomycin hydrochloride, and vinblastine sulfate. Heparin sodium has also been reported to be incompatible with cisatracurium besilate,[1] labetalol hydrochloride,[2] levofloxacin,[3] nicardipine hydrochloride,[4] reteplase,[5] and vinorelbine tartrate.[6] Although visually compatible,[7] cefmetazole sodium is reported to inactivate heparin sodium.

Glucose can have variable effects,[8,9] but glucose-containing solutions are generally considered suitable diluents for heparin. Incompatibility has also been reported between heparin and fat emulsion.

1. Trissel LA, *et al.* Compatibility of cisatracurium besylate with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1735–41.
2. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1048–51.
3. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; **56:** 1458–9.
4. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
5. Committee on Safety of Medicines/Medicines Control Agency. Reteplase (Rapilysin): incompatibility with heparin. *Current Problems* 2000; **26:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)
6. Balthasar JP. Concentration-dependent incompatibility of vinorelbine tartrate and heparin sodium. *Am J Health-Syst Pharm* 1999; **56:** 1891.
7. Hutching SR, *et al.* Compatibility of cefmetazole sodium with commonly used drugs during Y-site delivery. *Am J Health-Syst Pharm* 1996; **53:** 2185–8.
8. Anderson W, Harthill JE. The anticoagulant activity of heparins in dextrose solutions. *J Pharm Pharmacol* 1982; **34:** 90–6.
9. Wright A, Hecker J. Long term stability of heparin in dextrose-saline intravenous fluids. *Int J Pharm Pract* 1995; **3:** 253–5.

Units

The fifth International Standard for unfractionated heparin was established in 1998. The USP 31 states that USP and international units are not equivalent, although doses expressed in either appear to be essentially the same.

Adverse Effects

Heparin can give rise to haemorrhage as a consequence of its action. It can also cause thrombocytopenia, either through a direct effect or through an immune effect producing a platelet-aggregating antibody. Consequent platelet aggregation and thrombosis may therefore exacerbate the condition being treated. The incidence of thrombocytopenia is reported to be greater with bovine than porcine heparin.

Hypersensitivity reactions may occur, as may local irritant effects, and skin necrosis. Alopecia and osteoporosis resulting in spontaneous fractures have occurred after prolonged use of heparin.

Effects on the adrenal glands. Heparin inhibits the secretion of aldosterone and so may cause hyperkalaemia.[1] Although all patients treated with heparin may develop reduced aldosterone concentrations, most are able to compensate through the renin-angiotensin system. Patients on prolonged heparin therapy or those unable to compensate, such as patients with diabetes mellitus or renal impairment or those also receiving potassium-sparing drugs such as ACE inhibitors, may present with symptoms of hyperkalaemia. The UK CSM suggests[2] that plasma-potassium concentration should be monitored in all patients with risk factors, particularly those receiving heparin for more than 7 days. The hyperkalaemia is usually transient or resolves when heparin is stopped and treatment is not generally required; fludrocortisone was successfully used to treat resistant hyperkalaemia in a patient in whom continued heparin therapy was necessary.[3]

Adrenal insufficiency secondary to adrenal haemorrhage has also been associated with heparin; heparin-induced thrombocytopenia may be implicated.[4]

1. Oster JR, *et al.* Heparin-induced aldosterone suppression and hyperkalemia. *Am J Med* 1995; **98:** 575–86.
2. Committee on Safety of Medicines/Medicines Control Agency. Suppression of aldosterone secretion by heparin. *Current Problems* 1999; **25:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)